Report of the NCI-CDC Working Group to Revise

the 1985 NIH Radioepidemiological Tables

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I. Executive Summary

The legislative mandate for the 1985 Report of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables provided for analyses of existing data linking cancer risk to ionizing radiation exposure, to facilitate the adjudication of compensation claims for cancers diagnosed following exposure to ionizing radiation. The 1985 working group did this by estimating "probability of causation" (PC) values, defined as

$$PC = \frac{\text{Risk due to radiation exposure}}{\text{Baseline risk + risk due to radiation exposure}}$$

for hypothetical instances of cancer following specific histories of radiation exposure. The report has been used mostly by the Department of Veterans Affairs (VA) as a guide to adjudicating compensation claims for cancers diagnosed in persons who were exposed during military service. The amount of new information about radiation-related cancer risk has increased markedly during the 15 years since publication of the report, and there have been revisions in the system of dose reconstruction used for the major source of epidemiological data for estimating risk, the cohort of atomic bomb survivors studied by the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. The VA requested the Secretary of the Department of Health and Human Services (DHHS) to update the Report, as provided for in the original legislative mandate, and joined with the DHHS to support the present effort by a working group of the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC).

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Noting that the National Academy of Science/National Research Council (NAS/NRC) Committee on Biological Effects of Ionizing Radiation (BEIR VII, phase 2) is expected to complete within 2 or 3 years a comprehensive survey of the scientific data linking radiation exposure to health effects in human beings, the NCI and CDC have undertaken to provide an interim update of the 1985 report based on statistical analyses by the working group of readily available data on cancer risk following radiation exposure, notably the 1958-87 LSS Tumor Registry data on survivors of the atomic bombings of Hiroshima and Nagasaki made available on computer disk by RERF. It is expected that a further update to the present report will be made following the BEIR VII review. The working group has replaced the tabular format of the 1985 report by an interactive computer program (IREP, for "interactive radio-epidemiological program") that eliminates nearly all of the computational labor of estimating PC values and their uncertainties, and permits a more detailed and comprehensive expression of the various components of the calculation and their uncertainties.

It has been argued, notably by the NAS/NRC oversight committee that provided critical advice to the 1985 NIH working group (NAS, 1984), that the PC values calculated according to the formula given at the beginning of this summary pertain to populations rather than individuals, and that they "are not probabilities in the usual sense and are truly properties of the group to

which a person belongs, but in practice are assigned to the person for purposes of compensation." The oversight committee recommended a change in terminology, replacing "probability of causation," by "assigned share" (AS) to emphasize the difference. The NIH working group did not disagree, but continued to use "PC" because the term was already in common use. The present working group feels that the oversight committee's point is worth repeating, and has chosen to use "AS" throughout its report although "PC" is probably even more commonly used than in 1985. More generally, the working group emphasizes that the AS values obtained using the report and its computer program represent a summary of scientific findings about cancer risk following radiation exposure, that may be relevant to adjudication of individual claims, but that the report makes no claims regarding the influence of individual factors that have not been extensively studied.

It has also been argued by Greenland and others (Greenland, 1988, 1999; Robins, 1989a, 1989b; Beyea, 1999) that AS is a logically flawed concept, subject to substantial bias and therefore unsuitable as a guide to adjudication of compensation claims in cases of possibly radiation-related cancer. The argument is based largely on the possibility that radiation exposure may accelerate the time of appearance of cancers that, in the absence of exposure, would have occurred later. The conclusion of the present working group is that the argument may have theoretical merit but, as a practical matter, is unpersuasive in the light of current information about radiation-related risk. Scientific consensus about cancer risk following radiation exposure is constantly evolving as new information is uncovered. This is a time of rapid developments in our understanding of the carcinogenic process, and future developments may force a fundamental changes in our view of radiation carcinogenesis. For the present, however, the working group feels that current models are relevant both to radiation protection and the adjudication of claims for possibly radiation-related instances of cancer. Similar conclusions about the arguments of Greenland and others were reached by a an NAS/NRC subcommittee specially formed to review an earlier draft of the present report (NAS/NRC, 2000).

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The focus of this report is on quantitative expression of uncertainty in AS, reflecting statistical uncertainty about risk estimates and more subjective uncertainty about model assumptions necessary to apply such estimates to the adjudication of compensation claims for cancer diagnosed following radiation exposure in the United States. In the U.S., unlike the United Kingdom where a voluntary "Compensation Scheme for Radiation-linked Diseases" allows for proportional compensation for AS values as low as 20% Wakeford, 1998), adjudication of claims revolves around the likelihood that AS may exceed 50%. When there is a policy bias ("benefit of the doubt") in favor of the claimant, focus is on upper credibility limits for AS rather than on a central estimate. For example, present VA policy is to award claims for which the upper 99% credibility limit for AS is 50% or higher.

Uncertainty, including the statistical uncertainty inherent in estimates obtained by fitting

observational data to theoretical models and subjective uncertainty inherent in model assumptions, is the primary focus of this report. One of the many advantages of replacing tables by an interactive computer program is that much more detail can be made easily available to the user, including a complete representation of the uncertainty pertaining to a particular AS estimate.

The 1985 NIH report dealt with 13 different cancer sites for which there was strong statistical evidence of a radiation dose response in human populations. However, lack of a statistically significant dose response for a particular cancer type does not preclude a compensation award based on an upper credibility limit for AS. For example, the upper 99% credibility limit for AS can be greater than 50% even if the radiation dose response is not statistically significant (or even if, in extreme cases, the point estimate is less than zero). The present report is based on the working assumption that any type of cancer can, in principle, be induced by radiation, and that the most important question concerns the magnitude of the risk associated with particular exposures. In all, 27 different cancers and groups of cancers are treated, including several cancer types not significantly associated with radiation dose. The report does not include malignant melanoma and chronic lymphocytic leukemia, for which adequate data were lacking. Lung cancer associated with radon exposure is given separately from that associated with external exposure. The radon-related estimates are based on an analysis using data from a 1996 report to the U.S. Department of Justice (DOJ 1996). A more comprehensive analysis, based on the most authoritative risk estimates published by the NAS/NRC BEIR VI Committee (NAS, 1999), was judged not to be easily adaptable for AS purposes and to require more computational and staff resources than those available to the present working group. Finally, this report, like the 1985 report, does not address the health consequences of *in utero* exposure to ionizing radiation.

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Treatment of uncertainty in the updated report is guided by that in the original report and by more recent analyses, notably two publications of the National Council on Radiation Protection and Measurements (NCRP): Commentary 14 (NCRP, 1996), "A guide for uncertainty analysis and dose and risk assessments related to environmental contamination," and Report 126 (NCRP, 1997), "Uncertainties in fatal cancer risk estimates used in radiation protection." Essentially, the method involves calculation of an uncertain excess relative risk (ERR = excess risk/baseline risk) for the cancer of interest, as a function of radiation dose for each exposure. Other factors, represented by a series of randomly distributed factors which are assumed to be statistically independent, depend on informed but nevertheless subjective judgments from published reports of expert committees or by the authors of this report. They are designed to contribute bias correction and expression of additional uncertainty to a Monte Carlo simulation which provides a corrected ERR estimate, expressed as the product of all factors, and its uncertainty distribution combining all sources of uncertainty. If more than one exposure is involved, separate ERR values and uncertainty distributions are calculated for each exposure, and combined. The overall

ERR is then transformed to obtain the AS:

$$AS = ERR/(1+ERR).$$

Credibility limits for the AS are obtained as percentiles of its uncertainty distribution.

The various factors contributing to the overall estimate, and its uncertainty, are as follows:

ERR per unit of dose (or dose plus dose-squared) and its statistical uncertainty distribution are taken from the appropriate tabulated likelihood curve obtained as the final output of statistical model fitting performed by the working group. For most cancers, the ERR per unit of dose is allowed to depend on sex, age at exposure, and attained age (or, in the case of leukemia, time since exposure). The analysis specifically includes uncertainties in the parameters that quantify these dependencies. ERR per unit dose, as estimated, may be influenced by random and systematic errors in A-bomb survivor dosimetry, requiring several uncertain bias correction factors. Radiation dose for the claimant is entered by the user, either as a known value or as an uncertain value with a user-specified uncertainty distribution. Doses received at low doses and dose rates are adjusted by a factor (with uncertainty) known as the dose and dose rate effectiveness factor (DDREF), which may reduce the ERR per unit dose of gamma ray or other sparsely ionizing radiation. The DDREF does not apply to neutrons, alpha particles, or other kinds of densely ionizing radiation which are thought to have greater biological effects than sparsely ionizing radiation and are weighted accordingly. A separate term, the radiation effectiveness factor (REF), is used to express the differences in the biological effectiveness for various radiation types relative to the risk per unit dose induced by exposure to either acute or chronic exposures of high energy gamma radiation. As with the DDREF, uncertainty in the REF is expressed as a subjective probability distribution of possible values.

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Site-specific baseline risks for many cancers differ substantially between Japanese and US populations, and there is considerable uncertainty about how this affects risks resulting from radiation exposure. An uncertain and complex factor is required for transfer of risk estimates from A-bomb survivors to a US population. Tobacco smoking is known to modify the carcinogenic effects of radiation to the lung, also requiring an uncertain adjustment factor. Finally, an optional uncertainty factor is included for additional, documented factors that may be justified as pertaining to identifiable subpopulations.

The present report is considered to be an interim update of the 1985 NIH report. Like that report, its AS estimates are based primarily on A-bomb survivor data. The present working group has had the advantage of access to comprehensive cancer incidence data from a greatly improved RERF Tumor Registry; these data are not only more recent than those used previously but are based on more timely and more accurate diagnoses than those available from death certificates. Incidence data are also more relevant to compensation claims for cancers of delayed or low

fatality. Direct access to RERF data allowed the working group to conduct its own analyses directed at the needs of this report, including modeling of dose-response modifiers such as age at exposure, and inclusion of cancer types not significantly associated with radiation exposure.

Unlike the 1985 report, the current report is based on linear dose-response models for all solid cancers, with an uncertain DDREF factor to allow for the possibility that risk per unit dose decreases with decreasing dose and dose rate. This approach is not necessarily better than the linear-quadratic model approach used previously, but it is in accord with recent recommendations by expert committees. Also, the present report treats relative biological effectiveness of densely cf. sparsely ionizing radiation as an uncertain quantity, relying on a report of the National Institute for Occupational Safety and Health. The present report's treatment of the problem of transfer of estimates between populations with different baseline rates is an important change, and accounts for a large part of the total uncertainty for several sites.

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An early draft of this report was reviewed by a specially constituted subcommittee of the National Research Council's Committee on an Assessment of Centers for Disease Control and Prevention Radiation Studies from DOE Contractor Sites, namely, the Subcommittee to Review the Radioepidemiology Tables. That subcommittee, chaired by William J. Schull, released its report, entitled *"A Review of the Draft Report of the NCI-CDC Working Group to Revise the '1985 Radioepidemiology Tables,'"* on November 29, 2000 (NAS/NRC, 2000). As a result of that review, the Working Group has made a number of changes motivated by concerns expressed by the subcommittee about usability of the interactive computer program (IREP) by non-specialists, the omission of certain problematic cancer sites from the draft report, and inclusion of other sites for which the association between risk and radiation dose is not well established, e.g., because it is based on sparse data yielding very wide confidence bounds on dose-specific risk. The present report has also been influenced by recent legislation (Public Law 106-398: Energy Employees Occupational Illness Compensation Program Act of 2000) mandating the use of the 1985 NIH report, "as such tables may be updated from time to time under provisions of section 7(b)(3) of the Orphan Drug Act," for adjudicating claims related to cancers diagnosed in workers and former workers at Department of Energy facilities with histories of occupational exposure to ionizing radiation.

As previously mentioned, this is an interim report which is expected to be modified as new information on radiation-related risk becomes available. It is hoped that the *form* of the report may prove to be of more lasting value. In particular, the IREP program is constructed to allow - new risk estimates and statistical uncertainty distributions to replace old ones, for new cancer sites to be added, and for the treatment of other sources of uncertainty to be modified.

II. Background of 1985 report

A. Congressional mandate and its execution

On January 4, 1983 the President of the United States signed Public Law 97-414 (known as the "Orphan Drug Act"), an act to amend the Federal Food, Drug and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, and for other purposes. This legislation includes a provision (Section 7 (b) of the bill) directing the Secretary of Health and Human Services (DHHS) to "devise and publish radioepidemiological tables that estimate the likelihood that persons who have or have had any of the radiation-related cancers and who have received specific doses prior to the onset of such disease developed cancer as a result of these doses." The mandate included a provision for periodic updating of the tables.

It may be noted that the section of P.L. 97-414 pertaining to the development of radioepidemiological tables originally was introduced by Senator Orrin Hatch (Utah) as a part of Senate bill S 1483: "Radiation Exposure Compensation Act" to provide for damages due to radiation exposure from nuclear weapons tests in Nevada. Since neither this bill nor the companion House bill (H.R. 6052) was reported out of the respective committees, the section relating to radioepidemiological tables was attached as an amendment to the "Orphan Drug Act" which was passed by both houses and signed into law on January 4, 1983. The complete text of section 7 (b) of the bill and an excerpt from President Reagan's statement, on the occasion of his signing the Orphan Drug Act, are given in Appendix A of the present report.

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Lead responsibility for the implementation of the enacted charge was assigned to the National Institutes of Health (NIH) by the Assistant Secretary of Health, DHHS, who also requested that a National Research Council (NRC) committee be formed to review the recommendations of the NIH. Subsequently (August 4, 1983), the Secretary of Health and Human Services approved the Charter for an "Ad Hoc Working Group to Develop Radioepidemiological Tables" to carry out this mandate. The text of the Charter is included as Appendix B.

An Ad Hoc Working Group, chaired by Dr. J. E. Rall, Deputy Director for Intramural Research, NIH, was established to carry out the work. The NIH contracted with the National Academy of Sciences (NAS) for the formation of an Oversight Committee in the NRC's Commission on Life Sciences, with the cooperation of the Institute of Medicine. The oversight committee, chaired by Prof. Frederick Mosteller of Harvard University, reviewed the data sources, assumptions, and methods of the NIH working group, and discussed wider issues regarding the tables in the context of their intended and possible uses. The report of the oversight committee was published in 1984 and the report of the working group was published on January 4, 1985.

Subsequent to the 1985 publication, the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) published a report on "Use of Probability of Causation by the

Veterans Administration in the Adjudication of Claims of Injury Due to Exposure to Ionizing Radiation" (CIRRPC 1988). The CIRRPC report expanded on the uncertainty evaluation in the 1985 NIH report, and provided doses for screening claims, which have subsequently been used by the Veterans Administration.

B. "Assigned share"

The National Academy of Sciences committee charged with oversight of the 1985 NIH radioepidemiological tables report (NRC, 1984) objected to the use of the term "probability of causation," or "PC," for the ratio,

$$PC = \frac{\text{risk due to radiation exposure}}{\text{baseline risk} + \text{risk due to radiation exposure}}$$

$$= \frac{\text{excess relative risk}}{1 + \text{excess relative risk}}.$$

The NAS committee pointed out that a negative ERR would result in a negative "probability" (a defect easily remedied by specifying boundary conditions for PC) and, more seriously, that the ratio applied to populations and not individuals and could not be interpreted as the probability that a given cancer was caused by a given radiation exposure. They recommended using the term "assigned share" as a more appropriate term, because the computed quantities "are not probabilities in the usual sense and are truly properties of the group to which a person belongs, but in practice are assigned to the person for purposes of compensation." The present working group is sympathetic to this view and is in large part guided by it.

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C. Methodology used in the 1985 report

1. Data sources. Baseline rates were taken from U.S. cancer incidence data for 1973-81 (SEER, 1984), by sex but not by race, and averaged over time . Site-specific average excess rates were taken from the 1980 report of the NAS/NRC Committee on the Biological Effects of Ionizing Radiation (BEIR III) (NAS, 1980, Tables V-14 and V-16) and from other sources, as shown in Table II.C.1. Lymphoma, multiple myeloma, and cancers of the prostate gland, uterus and cervix, testis, and brain specifically were not covered, because of insufficient information and lack of a statistically significant dose response. Chronic lymphocytic leukemia (CLL) was considered to be unrelated to radiation exposure.

2. Dose-response models. Based on a review of the experimental and epidemiological literature, a specific linear-quadratic model was assumed for all of the sites tabulated above, with the exception of breast and thyroid gland, for which linearity was assumed. The linear-quadratic model for a single, acute exposure to sparsely ionizing radiation (low-LET, for low linear energy transfer) was that preferred by the BEIR III committee (NAS 1980, equation V-10),

$$\text{excess risk} = \alpha\,(D + D^2/1.16),$$

where D is dose in Gy and α depends upon site, age at exposure, and sex. The value of α was equal to the corresponding linear-model risk coefficient from BEIR III or other source, divided by 2.5. Excess risk associated with a chronic exposure, or with exposure to densely ionizing (high-LET) radiation, was assumed to be linear in dose, with coefficient α. Different exposures were considered to be additive in effect; that is, excess risks associated with radiation exposures at different times were calculated separately and summed.

3. Minimal latent period and distribution of risk over time following exposure. For leukemia and bone cancer, radiation-related risk was assumed to be distributed lognormally over time following exposure, with a minimal latent period of 2 years. The lognormal distributions differed by cancer type and subtype and (for acute leukemia) by age at exposure, and were obtained by fitting original data. For other cancers, excess risk was assumed to be proportional to age-specific baseline risk (i.e., ERR was assumed to be constant) beginning 10 years after exposure; it was further assumed that there was no risk up to 5 years following exposure, and that ERR increased from zero at 5 years to its full value at 10 years according to a symmetric, S-shaped cubic polynomial function of time.

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4. Dependence of excess risk on sex and on age at exposure. Following BEIR III, risk estimates were given separately by sex and age at exposure categories, regardless of statistical significance for these factors. Original estimates were in the form of excess (absolute) risk per unit dose, by sex and interval of age at exposure, averaged over a follow-up time of 5-26, 10-30, 10-33, 10-34, or 10-35 years, depending upon site; this corresponded to the data sets on which the estimates were based. Original estimates were converted to dose-specific ERR by dividing estimated excess risk by baseline risk, i.e., obtained as the lifetable-weighted average of age-specific SEER rates (SEER, 1984) over the same follow-up period. Thus, for sites where the excess risk estimate was based on Japanese A-bomb survivor data, and where U.S. and Japanese baseline rates differ, it was assumed that absolute risks, and not relative risks, averaged over the period of observation, were the same in the two populations.

5. Modification of ERR by other exposures and/or by host factors. The question of host factor modification was not addressed explicitly. Modification by other exposures was discussed generally, but specific recommendations were made only for tobacco smoking, in the case of lung cancer, and for radiation exposures other than those at issue. Different radiation exposures were treated as additive in effect, as discussed in II.C.1 above. Thus, the excess cancer rate corresponding to a second exposure was assumed to be independent of the excess cancer rate corresponding to an earlier exposure. Smoking and low-LET radiation were also considered to be additive in effect with respect to lung cancer causation, that is, the radiation-related excess rate was assumed to be independent of smoking history. Thus, a smoker would have a lower

excess relative risk associated with exposure than an otherwise similar nonsmoker, because the nonsmoker's baseline rate was smaller. However, smoking and alpha radiation from inhaled radon decay products were considered to be multiplicative in effect, i.e., computation of ERR for radon exposure did not depend upon smoking history, since excess risk due to radiation and baseline risk were assumed to be proportionally affected by smoking history.

D. Uncertainty

Sources of biased and unbiased uncertainties, and propagation of errors, were extensively discussed in Chapter VII of the 1985 report. Biased uncertainties included overestimation of (absolute) risk 5-14 years following exposure, and underestimation associated with use by the BEIR III committee (NAS, 1980) of the T65D dosimetry system (Kerr,1979) for estimating dose-specific risk among A-bomb survivors. (By 1983-84 it was clear that T65D was going to be replaced, but the new system, DS86 (Roesch, 1987), was not yet in place.) Unbiased uncertainty pertained to the use of baseline rates based on the entire region covered by the SEER registry, modeling of risk as a function of age at exposure, assumptions about dependence of risk on time following exposure, and assumptions about the curvature of the linear-quadratic dose-response curve estimated in BEIR III. Other sources of uncertainty were also discussed, but only those just noted were taken into account in computing combined uncertainty, represented by a geometric standard deviation value and a bias correction factor, for different cancer sites and years following exposure. The emphasis of the report was on point estimates; recommendations were given for modifying tabulated AS values to account for bias and uncertainty.

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CIRRPC (1988) also evaluated uncertainties in the PCs estimated in the 1985 publication. This assessment treated most uncertainties in the same way as the 1985 report, except that an evaluation of statistical uncertainty was added, uncertainty in evaluating age at exposure was increased, and additional probability was assigned to a linear dose-response.

The CIRRPC assessment was addressed primarily at providing doses for screening claims, and for this purpose, it was assumed that the claimant had a baseline risk at the 10^{th} percentile of the distribution of the baseline risks for the cancer of interest among all counties of the United States. Neither the 1985 publication nor CIRRPC evaluated uncertainty resulting from the use of the additive model for transferring risks from A-bomb survivors to the US population.

III. Reasons for update

A. New data, new findings

The original NIH report (NIH, 1985) was written in 1984, and based on data available at that time. Site-specific estimates of excess absolute risk (excess cases per 10^6 persons per year per rad), by interval of age at exposure, were obtained from the BEIR III report (NAS, 1980), which relied largely on A-bomb survivor mortality data for 1950-74 but also on other studies. The NIH report also used more recent risk coefficients from the A-bomb survivor Life Span Study (LSS) mortality report for 1950-78 (Kato and Schull, 1982) and site-specific, incidence-based studies of leukemia (Ichimaru, 1978), thyroid cancer (Parker, 1974, Ishimaru, personal communication), and preliminary data on female breast cancer (Tokunaga, 1987) in the same population. To a lesser extent, the report surveyed studies of cancer mortality in British patients given therapeutic radiation for ankylosing spondylitis (Smith and Doll, 1982), lung cancer among Czech, Canadian, Swedish and U.S. uranium miners (Jacobi et al, 1985), thyroid cancer in patients given x-ray epilation for treatment of tinea capitis (Ron and Modan, 1980), breast cancer among women given medical x rays (Boice, 1977, Shore, 1977), bone sarcoma among German patients treated for benign disease with injected radium (Mays, 1983), and estimates of salivary gland cancer risk in various irradiated populations (Land, 1986).

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In the succeeding 15 years, the dose reconstruction system for the A-bomb survivors has been revised, and a large amount of new information has been obtained relating radiation exposure to subsequent cancer risk. For example, the number of cancer deaths among members of the cohort of atomic bomb survivors followed by the RERF in Japan increased from 3842 in 1950-74 (Kato and Schull, 1982) to 7827 in 1950-90 (Pierce et al, 1996). Much of the newer information pertains to cohort members exposed during the first and second decades of life: as these survivors reached ages at which cancer rates normally become appreciable, the newer data supported statistically stable risk estimates not obtainable previously. The same is in general true for other exposed cohorts that include persons exposed at young ages. In the original NIH report it was possible to estimate risk of radiation-related cancer following exposure before age 10 and at ages 10-19 for leukemia and cancers of the female breast, salivary gland, thyroid gland, and bone, while lung and stomach cancer risk estimates were available for exposure at ages 10-19. For other sites covered by the report (esophagus, colon, liver, pancreas, and urinary cancers), no calculations were done for exposure ages less than 20.

In addition, national and international committees have evaluated the newer data and used them for risk assessment (NAS/NRC, 1990, ICRP, 1991, UNSCEAR, 1988, 1994). Although none of these evaluations take account of the latest data, they are based on more recent data than BEIR III and their existence and current use for radiation protection purposes underscores the fact that the estimates used in the 1985 NIH report are out of date. The risk estimates provided in ICRP

Report 60 (1991) (based on the UNSCEAR 1988 report), in particular, are widely used and are generally higher than those in the BEIR III report.

B. New availability of risk data at the level of incidence.

Perhaps the most important recent development, however, has been a remarkable improvement, by the Radiation Effects Research Foundation (RERF) and its collaborators in Hiroshima and Nagasaki, of the Life Span Study (LSS) Tumor Registry to a high level of accuracy and efficiency (Mabuchi, 1994). The LSS registry draws on hospital records and physician notifications accessed by the local tumor registries of Hiroshima City, Nagasaki City, and Nagasaki prefecture, pathology and hematology records through the Hiroshima and Nagasaki tissue registries, and the Leukemia Registry developed in the late 1940s and early 1950s, as well as the virtually complete system of mortality notification and ascertainment of death certificate diagnosis that is the basis of the LSS mortality studies of atomic bomb survivors. In general, incidence data, when they can be obtained, are superior to mortality data because they capture information on cancers of low or delayed fatality and because they are based on diagnostic information that is more detailed and more accurate than death certificate data.

C. The use of the NIH report today is somewhat different from that contemplated at the time the report was written.

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The circumstances of the legislation mandating the 1985 NIH report suggested that partial compensation for claims of radiation-related cancer might be made on the basis of assigned share estimates between 10% and 50%, whereas full compensation would apply for AS ≥ 50%. Thus, the main graphical displays in the report show computed, "best-estimate" AS values corresponding to organ doses of 1, 10, and 100 rad (0.01, 0.10, and 1.0 Gy), as a function of age at exposure and/or time following exposure, and the reader is referred to the chapter on uncertainty limits for instructions on how to compute them. In fact, the tort law concept of "at least as likely as not," corresponding to AS ≥ 50%, continues to dominate the language of claim adjudication, with the notable modification in some important applications that claims may be winnowed out only if there is little or no reasonable doubt that the true value of the AS is less than 50%. For example, the Department of Veterans Affairs (DVA) screens out claims for which the 99% upper limit for the AS is less than 50% (Dr. Neil Otchin, personal communication). This development suggests that any revision of the 1985 report should seek a more nearly complete expression of the scientific information related to risk of cancer following exposure to ionizing radiation, as it applies to particular cases. In other words, emphasis should be placed upon a comprehensive expression of uncertainty, and one that is easily accessible to the user.

At a fairly late stage in its development, the present report was overtaken by events in the form of the Energy Employees Occupational Illness Compensation Program Act (EEOICPA) of 2000 (Public Law 106-398). That law established new programs for assisting nuclear weapons

production employees who have work-related illnesses. These programs include a federal program, administered by the U.S. Department of Labor (DOL), for eligible employees with chronic beryllium disease, silicosis, and possible radiation-related cancers. The act requires that adjudication of claims for radiation-related cancers be based on the radiation dose received by the claimant (or a group of employees performing similar work) at such facility, and on a determination that a probability of causation (assigned share) value of 50% or greater is consistent with the appropriate upper 99 percent confidence limit in the radioepidemiological tables published by the NIH in 1985, "as such tables may be updated from time to time under provisions of section 7(b)(3) of the Orphan Drug Act." Thus, the decision rule used by the DVA to screen (and, in practice, to award) claims has now been accorded the force of law.

The CDC's National Institute of Occupational Safety and Health (NIOSH) has been charged with (1) providing information to the DOL on estimated radiation doses for claimants' past occupational exposures to radiation, in cases where exposure measurements are unavailable, incomplete, or of poor quality (dose reconstruction), and (2) providing advice on the scientific guidelines that DOL would use in determining whether it is at least as likely as not that an energy employee's cancer was caused by occupational exposure to radiation (determining the assigned share or probability of causation). The NCI-NIH working group, while working to respond to the recommendations of the NAS-NRC review committee, has had the benefit of discussions with members of the NIOSH Office of Compensation Analysis and Support. Mindful of its responsibilities under the EEOICPA of 2000, the NIOSH group made a number of suggestions for the revised report to address specific NIOSH requirements. These suggestions, and the working group's responses, are discussed in the body of the present report.

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D. New attention to cancer sites whose association with radiation exposure is tenuous.

The cancers covered by the 1985 NIH report were those for which a statistically significant radiation dose response had been demonstrated in one or more major analyses. Statistical significance is equivalent to having a positive lower confidence limit, at a certain confidence level, for dose-specific excess relative risk, and therefore also for the AS. The list of cancers fitting this criterion is not greatly different today, but it is clearly possible for an upper uncertainty limit for the ERR to be greater than 1, and hence for the corresponding AS limit to be greater than 50%, even when the estimated ERR is not significantly greater than zero. Thus a wider range of cancer sites is of interest than that covered by the 1985 report.

E. New analytical approaches and ways of summarizing data

The 16 years since the 1985 NIH report have seen enormous advances in accessible computing power, particularly at the level of personal computers, and the development and refinement of statistical packages for risk analysis. An important consequence is that statistical modeling of radiation dose response and its modification by factors such as gender, age at exposure, time

since exposure, age at observation for risk, smoking history, and reproductive history can be carried out far more quickly and easily than before. New analyses, tailored for particular applications like the subject of this report, are easily accomplished, especially since the most comprehensive LSS mortality and incidence data are available from the RERF web site, at http://www.rerf.or.jp. These data, grouped to protect the privacy of individual survivors, are those used in the 1950-90 mortality report (Pierce et al, 1996) and the cancer incidence reports based on RERF Tumor Registry and Leukemia Registry data through 1987 (Thompson et al, 1994, Preston et al, 1994). The AMFIT algorithm for Poisson model regression, part of the Epicure statistical package (Preston et al, 1991), is particularly well suited for cohort-based analyses of radiation-related risk and has become closely identified with analyses of A-bomb survivor data in particular. These statistical approaches were used, for example, to develop the models used in the BEIR IV, V, and VI reports (NAS, 1988, 1990, 1999).

F. More attention to uncertainty and presentation of risk

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The 1985 NIH report presented illustrative graphs of assigned share estimates, tables of coefficients for various components needed to compute assigned share, and algorithms for calculating assigned share from these coefficients for arbitrary values of radiation dose, age at exposure, and time following exposure. Statistical and other sources of bias and uncertainty were extensively discussed in a separate chapter, and estimates and algorithms were provided for calculating "credibility limits" (based on statistical and subjective measures of uncertainty) for estimates of assigned share. In the intervening years, additional attention has been paid to quantification of uncertainty in applications to radiation-related risk, and new approaches for evaluating uncertainty have been developed (NAS, 1990, NCRP, 1996, 1997, EPA, 1999). It seems clear that considerations of uncertainty are central to radiation protection and adjudication of claims for compensation in cases of disease following radiation exposure. It is equally clear that the concept is complex and not easily applied by non-specialists, and would benefit from a more user-friendly approach as indicated by the following example:

The major U.S. government user of the NIH report to date is the Department of Veterans Affairs (DVA) which in 1985 asked the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC) of the Office of Science and Technology Policy, Executive Office of the President, to provide guidelines on how the NIH report might be used credibly to assist in adjudicating a veteran's claim of radiation injury. The Science Panel of CIRRPC interpreted the DVA's charge as one of quantifying the likelihood that a specified "probability of causation" (assigned share) in the NIH report would not be exceeded, with an *a priori* chosen level of credibility (CIRRPC, 1988). Their solution was to tabulate, by type of cancer, gender, age at exposure, and other relevant factors, the organ doses at which the upper AS credibility limit was 50% ("as likely as not") at credibility levels 90%, 95%, and 99%, respectively. The solutions were proposed as possible screening doses for specific cancers, exposure ages and times

following exposure. The screening procedure was biased toward ensuring that a marginal claim by an exposed veteran would not be rejected at this stage of consideration, and it was assumed that a claim not eliminated by this screening process would be adjudicated on its merits, taking into consideration the many factors that pertain to an individual claimant, including the AS value calculated according to the NIH report.

G. Availability of interactive computer programs as an alternative to tabular presentation

The tabular presentation of the 1985 report allowed users to look up tabulated coefficients appropriate to particular claims, and to calculate assigned share using these coefficients according to simple algorithms presented in the report. Increased computing power has made it possible to calculate assigned share and its uncertainty directly, for individual claims, from the particulars of exposure history, disease, and other relevant factors. This results in quicker, easier, and less error-prone computation, with tabular and/or graphical output options.

H. Use of organ-specific equivalent dose, in sievert (Sv)

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The present report expresses organ-specific radiation dose in gray (1 Gy = 1 joule of energy per kilogram of tissue), instead of the quantity used in the 1985 report, the rad (1 Gy = 100 rad; equivalently, 1 cGy = 1 rad). The report expresses equivalent dose, which incorporates weighting factors to represent the biological effectiveness of different types and energies of radiations, in sievert (1 Sv = 100 rem, where the rem is the quantity used previously). For irradiation by high-energy photons, such as exposure to gamma rays from the atomic bombings of Hiroshima and Nagasaki, the biological effectiveness is taken to be unity, by definition, and dose and equivalent dose are numerically the same (e.g., 5 cGy = 5 cSv). However, for alpha particles, neutrons, and lower-energy photons and electrons, a given dose is assumed to correspond to a higher equivalent dose, and the relationship between equivalent dose and dose depends on the radiation type and sometimes its energy and dose level.

In the present report, it is assumed that the starting point for calculation of AS is a single value or set of values of tissue-specific equivalent dose expressed in Sv, and that equivalent dose was calculated from an estimated dose (Gy) in the tissue of concern using standard conversion factors (average quality factors or radiation weighting factors) developed for radiation protection purposes. The estimated tissue dose from each radiation type obtained using the standard conversion factor then is modified by a radiation effectiveness factor (REF) for that radiation type and energy to give an equivalent dose in Sv and its uncertainty for use in calculating AS. This equivalent dose differs from the value used as the starting point in that the REF is expressed as a probability distribution based on radiobiological data (Kocher et al., 2002), rather than a point value of a standard quality factor or radiation weighting factor used in radiation protection. Thus, the calculation of AS specifically takes account of the biological effectiveness of each radiation type and energy of concern and its uncertainty.

IV. Description of the Approach

A. Overview

1. Assigned Share

Assigned share (AS) for an individual who was exposed to radiation, and who has been diagnosed with a cancer thought to be related to such exposure, is given by

$$AS = ERR/(1 + ERR)$$

where ERR is the excess relative risk associated with the exposure(s) of interest. ERR is a function of radiation dose (possibly accumulated over a number of exposures), age(s) at exposure, type of cancer, age at diagnosis, gender, and other factors possibly related to baseline and/or radiation-related risk.

As previously mentioned (section II.B), the working group is sympathetic to the view expressed by the 1984 oversight committee report (NAS, 1984), that the ratio, called "probability of causation," or "assigned share" (which we prefer) applies to populations and not individuals and cannot, for lack of detailed information and the ability to understand its full implications, be interpreted as the probability that a given cancer was caused by a given radiation exposure. The working group views assigned share as an actuarial concept, useful for summarizing the existing scientific evidence bearing on the likelihood that prior radiation exposure might be causally related to cancer occurrence under various circumstances, and which may in fact be the best available information pertaining to a particular case. Similarly, a statistical life table is a useful device on which to base social contracts such as a life insurance contract. A life table is based on observed frequencies of deaths by age in a large population and, with detailed information, it is easy to define, and easier still to imagine, subgroups for which life-table predictions based on the larger population may perform poorly. Yet these departures do not detract from the practicability of basing decisions about annuities, insurability, and insurance rates on life table predictions in the absence of such detailed information.

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2. Sources of uncertainty

New emphasis is placed on uncertainty analysis (NCRP, 1996), specifically, estimating an uncertainty distribution for the ERR (and associated AS), as opposed to a single point estimate. ERR is expressed as the product of several factors, which are assumed to be statistically independent. Each factor is uncertain, and is specified by an uncertainty distribution. The specified uncertainty distributions depend to some extent on subjective judgments by expert committees and by the authors of this report. The overall uncertainty distribution of the desired ERR is obtained by Monte Carlo simulation. These simulations involve sampling from the uncertainty distributions for each of the factors (or sources) included, and are similar to those

conducted by the Environmental Protection Agency (EPA,1999) and the National Council on Radiation Protection and Measurement (NCRP,1997). A computer program, here called IREP (for interactive radio-epidemiological program), has been developed to conduct these simulations individually for any desired application, taking account of specific characteristics of both the exposure and of the exposed individual.

The sources of uncertainty that are included are listed below, with details given in the sections that follow and in the appendices.

1. Sampling variability in the estimated ERRs. Statistical analyses of A-bomb survivor cancer incidence data were performed to estimate the ERR and its associated statistical uncertainty for each type of cancer. Dose response was assumed to be linear for solid cancers, after dose-response analyses found no evidence of departure from linearity. For leukemia, dose response was assumed to be linear for densely ionizing radiation such as neutrons and alpha particles, and for sparsely ionizing radiation (e.g., gamma ray, x ray) delivered at low dose rates; but quadratic for acute exposures to sparsely ionizing radiation. For most cancer types, the dose response was allowed to depend on sex, age at exposure, and age at diagnosis. Sampling variability includes both uncertainty in the overall risk estimate and in estimated parameters that quantify these dependencies. Details are given in Section IV.D and Appendices C and D.

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2. Correction for random and systematic errors in A-bomb survivor dosimetry. The statistical uncertainty discussed in the preceding paragraph pertains to assigned share for a member of the LSS sample, or for another A-bomb survivor whose radiation dose was estimated by the same methodology. It would not pertain exactly to another irradiated population with identical baseline cancer rates, because any biased or unbiased uncertainties in the reconstructed radiation dose estimates for the A-bomb survivors would not apply to the second population. Thus, risk estimates are adjusted for random errors in the doses assigned to individual A-bomb survivors, and also to several potential sources of systematic bias in these doses. The latter include systematic underestimation of gamma rays for Hiroshima survivors, uncertainty in the weighting factor for neutrons, and uncertainty in the neutron component of the total dose. Details are given in section IV.E and Appendix D.

3. Extrapolation of risk from sparsely ionizing radiation to low doses and dose rates. Doses received at low doses and dose rates are adjusted by a factor known as the Dose and Dose Rate Effectiveness Factor (DDREF). The treatment of the uncertainty in this factor is described in Section IV.F and Appendix D.

4. Transfer of risk estimates to a US population. Baseline risks for many cancers differ substantially for Japanese and US populations, and there is considerable uncertainty about how risk estimates derived from observations on an exposed Japanese population should be applied to an exposed US population. The treatment of this source of uncertainty is described in Section

IV.G and Appendix D.

5. Biological effectiveness of different radiations. Densely ionizing radiation, with a high energy transfer per track length in tissue (high linear energy transfer, LET), such as protons, neutrons, and alpha particles and other heavy ions, generally has a greater biological effectiveness per unit dose than low-LET radiation, such as gamma rays, x rays, and beta particles. For radiation protection purposes, dose of high-LET radiation in Gy is weighted by a factor, called the radiation weighting factor (w_R), which depends on the type of radiation and sometimes its energy (ICRP, 1991). The resulting weighted dose, called equivalent dose, is in Sv and provides a common metric of biologically significant dose for all radiation types. There is no uncertainty about w_R, since it is a defined value for a particular radiation type for use in radiation protection. For purposes of estimating risk and AS, however, w_R may be only a rough approximation of the biological effectiveness, relative to low-LET radiation, which is required when risk coefficients derived from studies of populations exposed mainly to low-LET radiation are applied in cases of exposure to high-LET radiation. In addition, the biological effectiveness of low-LET radiations (photons and electrons) may depend on energy, and this is not normally taken into account in radiation protection. Thus, biological effectiveness generally depends on the radiation type, and sometimes its energy and level of dose, and is an uncertain quantity. Treatment of uncertainties in biological effectiveness of different radiation types based on uncertainties in radiobiological data, which is discussed in Section IV.H, relies on a separate report commissioned by NIOSH (Kocher et al., 2002).

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6. Modification by smoking history. Tobacco smoking and, to a lesser extent, exposure of nonsmokers to side-stream tobacco smoke are powerful risk factors for lung cancer, especially, and a number of other cancers as well. Studies of uranium miners suggest that risk of radiation-induced lung cancer is increased among smokers to a greater extent than among non-smokers, but that this increase is somewhat less than the increase associated with smoking alone (NAS, 1999). The interaction between radiation exposure and smoking history is discussed in Section IV.I.

The following additional sources of uncertainty have been considered by others, but are not evaluated here.

1. Diagnostic misclassification in A-bomb survivor data. Both the NCRP (1997) and EPA (1999) uncertainty evaluations were based on mortality data, for which diagnostic misclassification is a more serious problem than for the incidence data used for this report. Also, the present report focuses on specific cancers, and diagnostic accuracy may depend on the cancer type. Although there is undoubtedly uncertainty resulting from diagnostic misclassification, it would be very difficult to quantify, and it does not seem likely that this uncertainty would be large relative to many of the other sources considered.

2. Extrapolation of risk beyond the time period covered by data. The focus of NCRP Report 126 (1997) was lifetime cancer mortality risk associated with radiation exposure, and the report specifically treated uncertainty about extrapolation of risk beyond the period of observation for risk. The concern was that the A-bomb survivor mortality data for 1950-1985 represented follow-up only until 40 years after exposure, whereas those data were being used to estimate lifetime risk for persons exposed at various ages including children whose expected remaining lifetime when exposed was 50, 60, 70, or more years. The NCRP report included a factor whose uncertainty contributed 6.7% of the overall uncertainty to *lifetime* mortality risk for a population of all ages at exposure, and 0.5% for a working population 20-65 years of age at exposure.

The present report is subject to the same problems of projection of risk beyond the period of observation, even though the vast majority of claims for which the report might be relevant are expected to pertain to adult exposures, for which such projection contributes little compared to other sources of uncertainty. However, (uncertain) trends in time since exposure (leukemia) or attained age (solid cancers), which address some of the same issues, were specifically included in the set of variables used to model radiation-related risk for different kinds of cancer, and were retained in the model as appropriate on statistical grounds.

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B. Sources of data

Although much new information on radiation-related risk in human populations has been published in the 15 years since the 1985 NIH report was prepared, the present report relies primarily on analyses by the Working Group of A-bomb survivor incidence data. The approach involved direct calculation of risk estimates and their statistical uncertainties from original data, in this case from the RERF Tumor Registry for 1958-87 (Thompson et al, 1994) and the RERF Leukemia Registry for 1950-1987 (Preston et al, 1994). Thyroid cancer received a more widely-based approach, involving a new analysis of the original thyroid cancer data from the international, pooled study of Ron et al (1995). Radon-related lung cancer risk estimates were computed by the Working Group using data and statistical models consistent with those used for a Department of Justice report (DOJ, 1996). Dale Preston, Chief of Statistics at the RERF, provided estimates for non-melanoma skin cancer based on the original data from a published study (Ron et al, 1998).

C. Choice of cancer types and approach to cancer types.

Adjudication of compensation claims for possibly radiation-related cancer is usually specific to organ site and often to histological type, and for this reason, models need to be developed for estimating risks for cancer of specific sites. Sites for solid tumor incidence data from the RERF Tumor Registry, as tabulated by Thompson et al (1994), are reproduced in Table IV.C.1, and sites for hematopoietic cancers from the Leukemia Registry, as tabulated by Preston et al (1994) are reproduced in Table IV.C.2. The final column of each table indicates grouping and other

treatment of each site for the present report. Estimates of the ERR per unit of exposure for site-specific cancers are often imprecise, especially for less common cancers. The need to estimate parameters that allow for modification of risk by sex, age at exposure, and attained age adds to the difficulty. In the approach described below, we have tried to strike a balance between allowing for differences among cancer sites and statistical precision.

For solid cancers, the general approach to defining categories was to provide separate estimates for each cancer site represented in the LSS data set by 50 or more cases among A-bomb survivors exposed to >5 mSv. Categories (with their ICD codes) that met this criterion were oral cavity and pharynx (140-141), esophagus (150), stomach (151), colon (153), rectum (154), liver (155.0), gallbladder (155.1, 156), pancreas (157), lung (162), female breast (174), uterine cervix (180), ovary (183), prostate (185), bladder (188), and nervous system (191,192). Thyroid cancer (193) and non-melanoma skin cancer (173) also met this criterion but for those sites more extensive data from Ron et al. (1995), and Ron et al. (1998) were used. To allow inclusion of additional categories that did not meet this criterion, uterine cervix was merged with other female genital cancers except ovary (179-182, 184), and prostate was merged with other male genital cancer (185-187). There was little or no evidence of dose-response for any of these cancers (Thompson et al, 1994). Additional categories for which estimates are provided are all digestive cancers (to be used for digestive cancers not included above, i.e. ICD codes 152, 158, 159); all respiratory cancers excluding lung (160-161, 163-165); all urinary cancers (to be used for kidney (189)); and a residual group of solid cancers (170-172, 174-males, 175, 190, 194, 195).

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For hematopoietic cancers, estimates are provided for each category shown in Table IV.C.2, even though the number criterion used for inclusion of solid cancer sites was met only for the largest grouping of leukemia types. Chronic lymphocytic leukemia (CLL) was specifically excluded from the risk calculations because of a lack of data on which to base an estimate. CLL is almost absent among Japanese generally and among the A-bomb survivors in particular (Parkin, 1997, Preston, 1994), but occurs frequently in Western populations, especially at older ages (Parkin, 1997). It has not, however, been associated with radiation exposure in studies of irradiated Western populations (NAS, 1990). Lymphoma and multiple myeloma are grouped together and treated in a manner similar to that for solid cancers as discussed below.

Radon-related lung cancer, although included in the 1985 NIH report, was not covered by the initial version of the present report because adaptation of the BEIR VI report (NAS 1996) for this purpose was felt to be beyond the resources of the Working Group. Inclusion was recommended by the NRC review subcommittee, and by government agencies (notably NIOSH) likely to use the revised report to adjudicate compensation claims. It was pointed out by the NRC review subcommittee (NAS-NRC, 2000) that Appendix A of a 1996 report prepared for the Department of Justice (DOJ, 1996) contains tables of cumulative radon exposures, in working level months (wlm), consistent with point estimates and upper 80% and 90% confidence limits for probability of

causation greater than or equal to 50%. The original data set used for these calculations, restricted to exposures ≤ 3200 wlm, was used by the Working Group to model lung cancer risk as a function of cumulative radon exposure.

D. Estimation of risk coefficients and their statistical uncertainties

1. Solid cancers from the RERF tumor registry report data.

In the models described in this section, thyroid cancer and non-melanoma skin cancers are excluded, and the term "all solid cancers" is used throughout to indicate solid cancers (ICD 140-199) without these two cancers. Site-specific baseline risks were modeled by stratifying on gender, city of exposure (Hiroshima or Nagasaki), calendar time, and attained age using the general approach described by Pierce at al. (1996). The following linear dose-response function was used to model the ERR:

$$ERR(D,s,e,a) = \alpha D \exp[\beta I_s(sex) + \gamma f(e) + \delta g(a)]$$

or, equivalently for $\alpha>0$, (IV.D.1)

$$ERR(D,e,a) = D \exp[\log(\alpha) + \beta I_s(sex) + \gamma f(e) + \delta g(a)],$$

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where D is dose in Sv, $I_s(sex)$ is an indicator function for the *opposite* sex (i.e., $I_s(sex) = 1$ for females and = 0 for males if s corresponds to "male", and conversely if s corresponds to "female"), e is age at exposure in years, a is attained age in years, f and g are specified functions of e and a, respectively, and α, β, γ, and δ are unknown parameters. The term $\beta I_s(sex)$ in expression (IV.D.1) is a computational convenience that allows the ratio between sex-specific estimates to be determined using site-nonspecific data, as discussed later. Based on published analyses of the RERF incidence data for 1958-87 with $f(e) = e$-30 and $g(a) = \log(a/50)$ (Thompson, 1994), it would not be necessary to include both age at exposure and attained age, for most sites, in a parsimonious model. However, it is our understanding that updated cancer incidence and mortality data, currently being evaluated at RERF, indicate a more general need for both variables (D. Preston, personal communication). In addition, the NAS/NRC review of an earlier draft of this report recommended models that allowed for attenuation of risk with time. The parameter δ in our general model (IV.D.1) allows for such attenuation.

The following specifications for the functions $f(e)$ and $g(a)$ were evaluated, and specification C was chosen for reasons discussed in the next paragraph.

A: $f(e) = e - 30,\ g(a) = \log(a/50)$;

B: $f(e) = min(e - 30, 0),\ g(a) = min(\log(a/50), 0)$;

C: $f(e) = min(max(-15, e - 30), 0),\ g(a) = min(\log(a/50), 0)$,

where "min" denotes "minimum" and "max" denotes "maximum".

The chosen specification (C) for $f(e)$ and $g(a)$ can also be written as follows:

$$f(e) = -15 \text{ for } e \le 15, = e - 30 \text{ for } e \text{ between } 15 \text{ and } 30, \text{ and } = 0 \text{ for } e > 30;$$

$$g(a) = \log(a/50) \text{ for } 0 < a < 50, \text{ and } = 0 \text{ for } a \ge 50. \qquad \text{(IV.D.2)}$$

When fitted to data for all solid cancers, the deviance values for models using the specifications A, B, and C were 3746.94, 3746.52, and 3743.15, respectively, with smaller deviance values indicating a closer fit of model to data. The nearly identical fits of models using A and B indicate that there is no direct evidence of modification of the ERR for exposure ages over 30 or attained ages over 50, and the somewhat better fit of model C indicates a lack of direct evidence of variation of the ERR by exposure age under 15. The model using C was chosen for application to solid cancers because it provided a better fit than the other two and because it allowed more statistically stable estimates at the extremes of exposure ages and attained ages. Exceptions were cancers of the thyroid gland and skin, as discussed at the end of section IV.D below. The chosen model, as fitted to the data, has the properties that, for fixed attained age, log(ERR/Sv) is constant (at different levels) for exposure ages less than 15 years and greater than 30, and decreases linearly with exposure age between 15 and 30. For fixed exposure age, log(ERR/Sv) decreases linearly with log(age) until age 50, and remains constant thereafter. With this choice of f and g, the parameter α represents (sex-specific) ERR/Sv for exposure age 30 or older and attained age 50 or older, since both f and g are zero for these ages. For exposure age e younger than 30 and/or attained age a younger than 50,

$$\text{ERR/Sv} = \alpha \times h(e, a; \gamma, \delta),$$

where

$$h(e, a; \gamma, \delta) = \exp\{\gamma f(e) + \delta g(a)\}$$

and where $f(e)$ and $g(a)$ are defined above according to specification C (IV.D.2).

The approach used to model parameters for site-specific cancers is similar to that used by Pierce and Preston (1993). With this approach, the parameters β, γ, δ, are estimated using data on all solid cancers, and these common values are then used for site-specific cancers unless there is evidence that the site-specific values differ significantly from the common values. In the application here, common values of the parameters γ and δ were used for all site-specific cancers with the exception of lung cancer and female genital cancers other than ovary. For lung cancer, a model with no age effects ($\gamma = \delta = 0$) provided a nearly identical fit to that obtained when both parameters were estimated, with some evidence of departure from the common values ($p = .12$ based on 2 d.f.) For female genital cancers other than ovary, a model with no age effects was also used; in this case, the estimated ERR/Sv was negative, and the fitted model would not

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converge with the common age parameters. Although there was modest evidence that the attained age effects were stronger for nervous system cancers and the residual category of all other cancers, data for these sites were judged too sparse to support separate estimates. For all other sites, p-values testing the appropriateness of the common values exceeded 0.2.

The parameters for the main effects (α) were estimated using only data on the cancer site of interest with γ and δ set equal to their common values . For cancers of the stomach, colon, and lung, the gender effect (β) was also estimated in this manner. For liver cancer, it was assumed that the ERRs for the two sexes were the same ($\beta = 0$), a result supported by Cologne et al (1999). For all remaining non-sex-specific cancers, the gender parameter obtained in an analysis of all non-sex-specific solid cancers combined was used; this value was $\beta = 0.843$, which corresponds to a female/male ratio of 2.3. In no case was there evidence of significant departure from this common value.

To evaluate the uncertainty in the estimated ERR/Sv for each sex at the various exposure and attained ages, it was necessary to consider the uncertainties and dependencies among the estimated parameters α, β, γ, and δ. To accomplish this, an approach known as joint analyses (Pierce and Preston 1993) was used. This approach allows one to estimate some parameters that are common to two or more cancer sites, and other parameters that differ by site. It also allows one to evaluate the resulting uncertainties and correlations of the estimated parameters. In the applications used here, separate main effects were estimated for (1) the specific cancer (or group of cancers) of interest, and (2) all solid cancers excluding the specific cancer of interest. All data were used to estimate γ and δ. For cancer categories where the common gender effect was used, the second group was further subdivided into non sex-specific and sex-specific cancers; only non-sex-specific cancers were used to estimate β.

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A possible approach for evaluating the uncertainty in the estimated ERR/Sv for each sex at various exposure and attained ages would have been to conduct joint analyses as described above, defining the parameters so that α reflected the ERR/Sv associated with a particular sex/exposure age/attained age, and obtain the profile likelihoods for the fitted α. However, this would have been extremely cumbersome (with slow computational speed) to implement in IREP, the interactive computer program for applying the algorithms developed by the working group.

In the interests of improving the computational speed of IREP, two approaches were used to estimate the unknown parameters α, γ, and δ and the statistical uncertainty distribution of ERR/Sv. In approach 1, the statistical uncertainty distribution was approximated by applying lognormal assumptions to the point estimates and covariance matrix for the three estimated parameters, $\log(\alpha)$, γ, and δ. This was done for five different site-sex combinations with relatively large numbers of cases and strong evidence of effects: all digestive cancers (male and female), stomach cancer (female), liver cancer (combined sexes), and female breast cancer.

These cancers contributed most strongly to the common estimates of γ and δ, and the correlations of $\log(\alpha)$ with γ and δ were therefore somewhat higher than for other sites. Also, the statistical likelihood distribution of ERR/Sv was closely approximated by a lognormal distribution. The means, variances, and covariances of the uncertainty distributions for the parameter estimates are shown in Table IV.D.1. For each of these site-sex combinations, the geometric mean (GM) and geometric standard deviation (GSD) of the statistical uncertainty distribution of ERR/Sv, evaluated at exposure age e and attained age a, are given by

$$GM = \alpha \times h(e, a; \gamma, \delta), \qquad \text{(IV.D.3)}$$

$$GSD = \exp\{[\mathrm{var}(\log(\alpha)) + \mathrm{cov}(\log(\alpha), \log(h(e, a; \gamma, \delta))) + \mathrm{var}(\log(h(e, a; \gamma, \delta)))]^{1/2}\},$$

where

$$\mathrm{cov}(\log(\alpha), \log(h(e, a; \gamma, \delta))) = \mathrm{cov}(\log(\alpha), \gamma) f(e) + \mathrm{cov}(\log(\alpha), \delta)\, g(a),$$

$$\mathrm{var}(\log(h(e, a; \gamma, \delta))) = \mathrm{var}(\gamma) f(e)^2 + 2\,\mathrm{cov}(\gamma, \delta) f(e) g(a) + \mathrm{var}(\delta) g(a)^2.$$

Approach 2 was used for all other solid cancer sites, with the exceptions of thyroid cancer and non-melanoma skin cancer for which the analyses were based on different data sets. For the sites treated using approach 2, correlations of $\log(\alpha)$ with γ and δ were not [illegible] (Appendix C), and it was considered appropriate to base the uncertainty evaluation on the assumption that α was independent of γ and δ. The fitting process was repeated, this time with parameters γ and δ set equal to the common values obtained from a fit for all solid cancers: $\gamma = -0.05255$ and $\delta = -1.626$. Thus, the site-specific and sex-specific dose effect α was estimated assuming no correlation of $\log(\alpha)$ with γ and δ. For non-sex-specific cancers, joint analyses were used with a common gender parameter (β) and separate main effects (α) for the cancer of interest and remaining non-sex-specific cancers. Inclusion of data for other, non-sex-specific solid cancers served to stabilize the male/female ratio of dose coefficients for males and females. Statistical uncertainty distributions for cancers treated using approach 2 are calculated in IREP by Monte Carlo simulation based on the statistical likelihood profile distribution for $\log(\alpha)$, given in Table IV.D.2 for most sites for which approach 2 was used, and a lognormal distribution for $h(e, a; \gamma, \delta)$, which is assumed to be statistically independent of α with

$$GM = \exp\{-0.05255\, f(e) - 1.626\, g(a)\},$$

$$GSD = \exp\{[0.0003261 \times f(e)^2 - 0.007297 \times f(e) \times g(a) + 0.5648 \times g(a)^2]^{1/2}\}.$$

For lung cancer and female cancers other than ovary, for which γ and δ were assumed to be zero, the statistical uncertainty distributions of log(ERR/Sv) are completely specified by the likelihood profile distributions for $\log(\alpha)$, as shown in Table IV.D.3.

For $e < 30$ and/or $a < 50$, some bias is associated with the assumption of statistical independence

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between the linear dose response parameter estimate α and the age-modifier parameter estimates γ and δ, provided the latter two parameters are not assumed to be zero. This bias is a function of e and a, and of the correlations between $\log(\alpha)$ and γ and between $\log(\alpha)$ and δ. As discussed in detail in Appendix C, approach 2 usually overestimates the upper 99% uncertainty for AS, sometimes by as much as 6% (e.g., estimating an upper limit of 53% instead of 50%) for some of the sites in Table IV.D.2 for which the correlation between $\log(\alpha)$ and γ approaches 0.25. For male colon cancer and male urinary organs other than bladder (for which the correlation between $\log(\alpha)$ and δ is between -0.06 and -0.08), and then only for e around 30 and a around 40, the upper limit may be underestimated by as much as 1% (e.g., as 49.5% instead of 50%).

Lymphoma and multiple myeloma, combined into a single group because of small numbers for multiple myeloma, were also evaluated in the manner indicated above, although these cancers were not included in the all solid cancer group used to estimate the common modifying effects. For this category, the ERR for males was positive, while that for females was negative. For the model here, it was assumed that the ERRs for the two sexes were the same although there was a suggestion that they differed ($p = .09$). The common age parameters were used since there was little evidence of departure from these values.

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As discussed above, a separate risk estimate was not computed for bone cancer because there were too few cases in the RERF data set. The working group suggests using the residual category estimate for this site.

2. Leukemia.

Site-specific baseline incidence was modeled as a function of gender, city of exposure (Hiroshima or Nagasaki), year of birth, calendar time (where indicated), and age at observation for risk (attained age), as discussed in Preston et al (1994). Default dose-response models were linear (proportional to dose equivalent D in Sv, henceforth called "dose" for brevity) for leukemia associated with exposure to high-LET radiation or low-LET radiation delivered at low dose rates (chronic exposure), and linear-quadratic for leukemia associated with acute exposure to low-LET radiation. The quadratic model was set to have equal contributions of the dose and dose-squared terms at 1 Sv (proportional to $D+D^2$). Fitting a general linear-quadratic (proportional to $D+\zeta D^2$) for all types of leukemia except chronic lymphocytic (CLL) considered as a group, and for acute myelogenous, acute lymphocytic, and chronic myelocytic leukemia separately, various estimates of the unknown parameter ζ were obtained, depending on the type of leukemia, that were greater than zero. However, since all these estimates were statistically consistent with the default value $\zeta=1$, the final models for leukemia and its subtypes were based on $\zeta=1$.

In terms of potential modifying factors such as sex (s), age at exposure (e), attained age (a), and time since exposure (t), the fitted model was

$$\mathrm{ERR}(D,e,a) = (D+D^2)\exp[\log(\alpha) + \beta I_{sex}(s) + \gamma e + \varepsilon t), \qquad \text{(IV.D.4)}$$

where α, γ, and ε are unknown parameters. Parameter α was estimated from the data, as were parameters γ, and ε unless they made no significant contribution to improvement of the fit of the model to the data, in which case they were set to zero. (Following Preston (1994), the leukemia dose response was modeled terms of e and $t = a - e$ instead of e and a.)

Unlike the approach for solid cancers, likelihood profiles for $\log(\mathrm{ERR}_{1Sv})$ were computed for different combinations of sex, exposure age, attained age, and/or time following exposure, as follows: The parameter α corresponds to the excess relative risk when $D+D^2 = 1$, $e=0$ and $t=0$. Thus (for example) the estimated ERR at 1 Sv (ERR_{1Sv}) for leukemia (all types except CLL) among females exposed at age 20 and observed 27 years following exposure can be obtained by replacing e by $e^* = e - 20$ and t by $t^* = t - 27$. The statistical uncertainty distribution of the resulting estimate is described by the profile likelihood distribution of the fitted parameter α. (Tables IV.D.4-IV.D.7). In practice, profile likelihood distributions were computed for formulations of e^* and/or t^* corresponding to various ages and times, and obtained by interpolation for intermediate values.

For leukemia of all types (Table IV.D.4), ERR_{1Sv} was modeled as a function of e and t, but not sex; for acute lymphocytic leukemia (ALL; Table IV.D.5), ERR_{1Sv} was modeled by t for $e < 20$ but for all ages combined for $e \geq 20$, as in Preston (1994); for acute myelogenous leukemia (AML; Table IV.D.6) and chronic myelogenous leukemia (CML; Table IV.D.7), modeling was by time since exposure and, for CML, sex.

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3. Thyroid cancer.

Thyroid cancer risk, estimated from the combined analysis data used by Ron et al (1995), required special handling because the data were from 6 different study populations (treating Hiroshima and Nagasaki survivors separately) with possibly different baseline and excess risks. There was no statistically significant dependence of ERR on gender or attained age, and the common attained age parameter value used for most solid cancers was statistically inconsistent with these data; therefore parameters β and δ were both set equal to zero. The final model was

$$\mathrm{ERR}(D,e) = D\exp(\theta_1 I_1 + \ldots + \theta_6 I_6 + \gamma e),$$

where $I_1, \ldots, I_6$ are indicator functions for the 6 study populations and where $\theta_1, \ldots, \theta_6$ are assumed to be normally distributed random variables with common mean θ. Parameter estimates $\boldsymbol{\theta_1, \ldots, \theta_6}$ and γ, and their estimated asymptotic covariance matrix, were obtained by Poisson regression (Hirosoft). The parameter estimate $\boldsymbol{\theta}$ was calculated as the mean of $\boldsymbol{\theta_1, \ldots, \theta_6}$, weighted by the inverse of their estimated covariance matrix $\boldsymbol{\Sigma}$. The off-diagonal elements of $\boldsymbol{\Sigma}$ were positive, indicating that $\boldsymbol{\theta_1, \ldots, \theta_6}$ were positively correlated.

The variance of the estimate θ was adjusted for nonhomogeneity of study populations by the method of DerSimonian and Laird (1986) for meta-analysis of clinical trials, as adapted by Ron et al (1995). The method assumes statistical independence among estimates obtained from different studies, a condition that was not strictly met in the present analysis because a common age-at-exposure parameter was used for the several studies. Since individual study estimates were positively correlated, use of the method is likely to have overestimated the variance of θ and thus resulted in overestimates of the upper uncertainty limits for ERR_{1Sv}.

The statistical uncertainty distribution for θ was assumed to be normal with mean and variance equal to θ and its estimated (adjusted) variance, respectively. $Log(ERR_{1Sv})$ for any given exposure age e_0 was estimated as θ, calculated with e defined as exposure age - e_0 (so that $e = 0$ for exposure age e_0) and was assumed to have a normal uncertainty distribution with GM and GSD as shown in Table IV.D.8 for e_0 in increments of 5. The logarithm of GM is linear in e_0, whereas log(GSD) is markedly curvilinear in e_0 for $e_0 < 20$.

Thyroid is the only cancer site in this report for which the dose-response data were primarily from populations exposed to medical x ray.

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4. Skin cancer.

The working group was reluctant to include skin cancers in the present report, because of a high level of uncertainty about how to transfer estimates of ERR/Sv between the Japanese A-bomb survivors and populations in the United States. Non-melanoma skin cancer is not a reportable disease in the United States (although it is in Japan), and baseline rates are not readily available, e.g., from NCI's SEER program (SEER, 1997). However, the NRC review committee report (NRC, 2000) pointed out that estimated rates were available for white and African-American US residents (Scotto, 1983), and recommended that the working group seriously consider including skin among the cancer sites covered by the present report. Also, both DVA and NIOSH expressed interest in having skin cancer estimates.

Our data source was the data set of Ron et al (2000), located at the RERF in Hiroshima. Dale Preston, RERF Chief of Statistics, kindly offered to run analyses for the working group. We initially asked for analyses similar to those for other solid tumors, i.e., using the general model used in Thompson et al, and the model specified in (IV.D.1) and (IV.D.2) of the present report.

For basal cell skin carcinoma, the only subtype for which a significant dose response was obtained by Ron et al (2000), there was a steep decline in ERR/Sv by exposure age, which extended beyond age 30 and was otherwise different from the common trend assumed for other sites, and there was no dependence on attained age. We therefore replaced the age function $f(e)$ specified in (IV.D.2) by

$$f(e) = \min(\max(-30, e-40), 0),$$